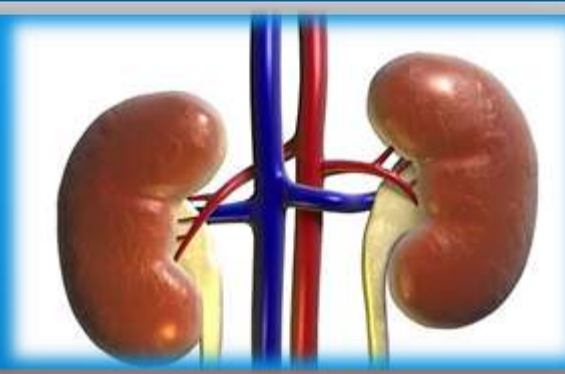


HYPERURICEMIA & THE KIDNEY

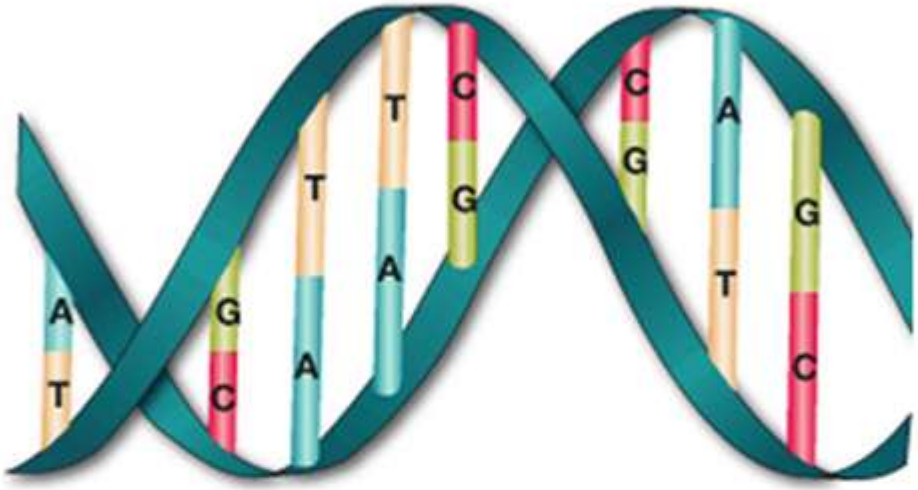
By

ESSAM NOUR ELDIN MD

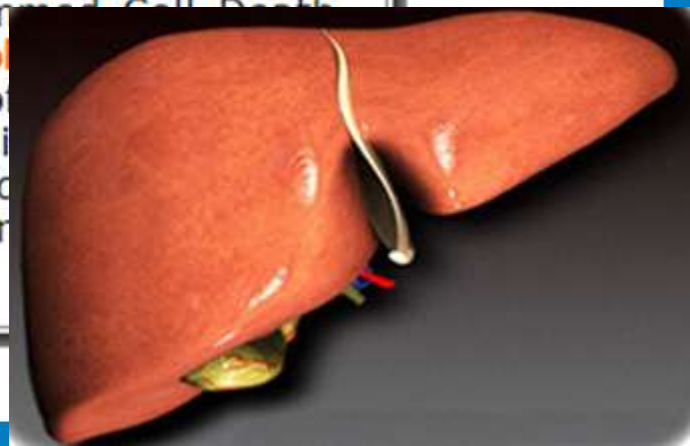
NEPHROLOGY DPT

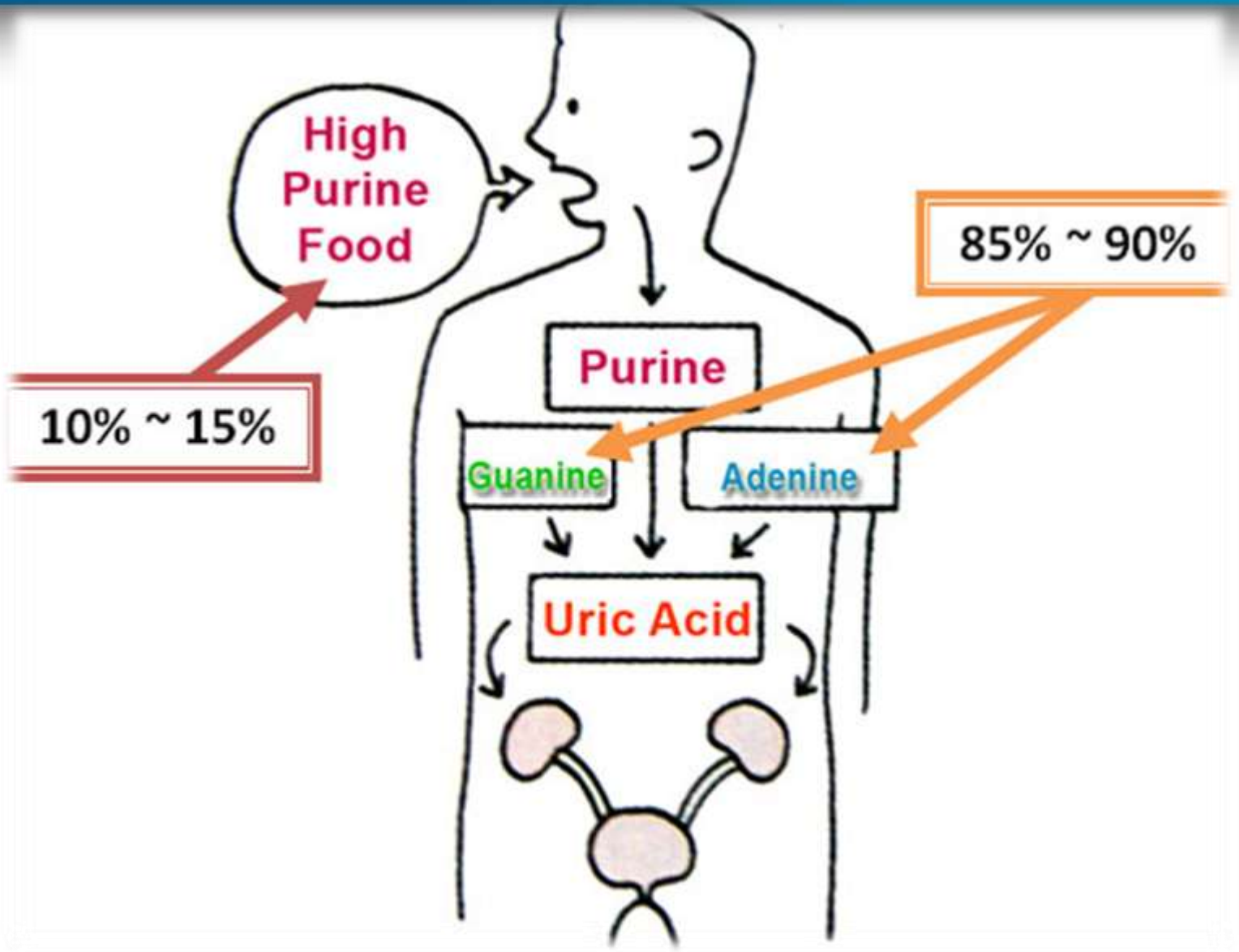
AIN SHAMS UNIVERSITY

DNA - DeoxyriboNucleic Acid



Out of the 4 bases: **adenine (A)**, cytosine (C), **guanine (G)** and thymine (T) found in DNA, 2 of them (Adenine & Guanine) contain **purine**. In average human adult, there are between **50 and 70 Billion** cells die Each Day due to the Apoptosis or Program
These death cells release **trillions** of **purine mo**
bloodstream. Some will be re-used in the formation o
most of the DNA-produced purines are sent to the li
down into **uric acid** for disposal through the kid
explains why liver meat is on top the list of high purin




High Purine Food
10% ~ 15%
85% ~ 90%
Purine
Guanine
Adenine
Uric Acid

Internal Purine Input
From DNA
85% ~ 90%

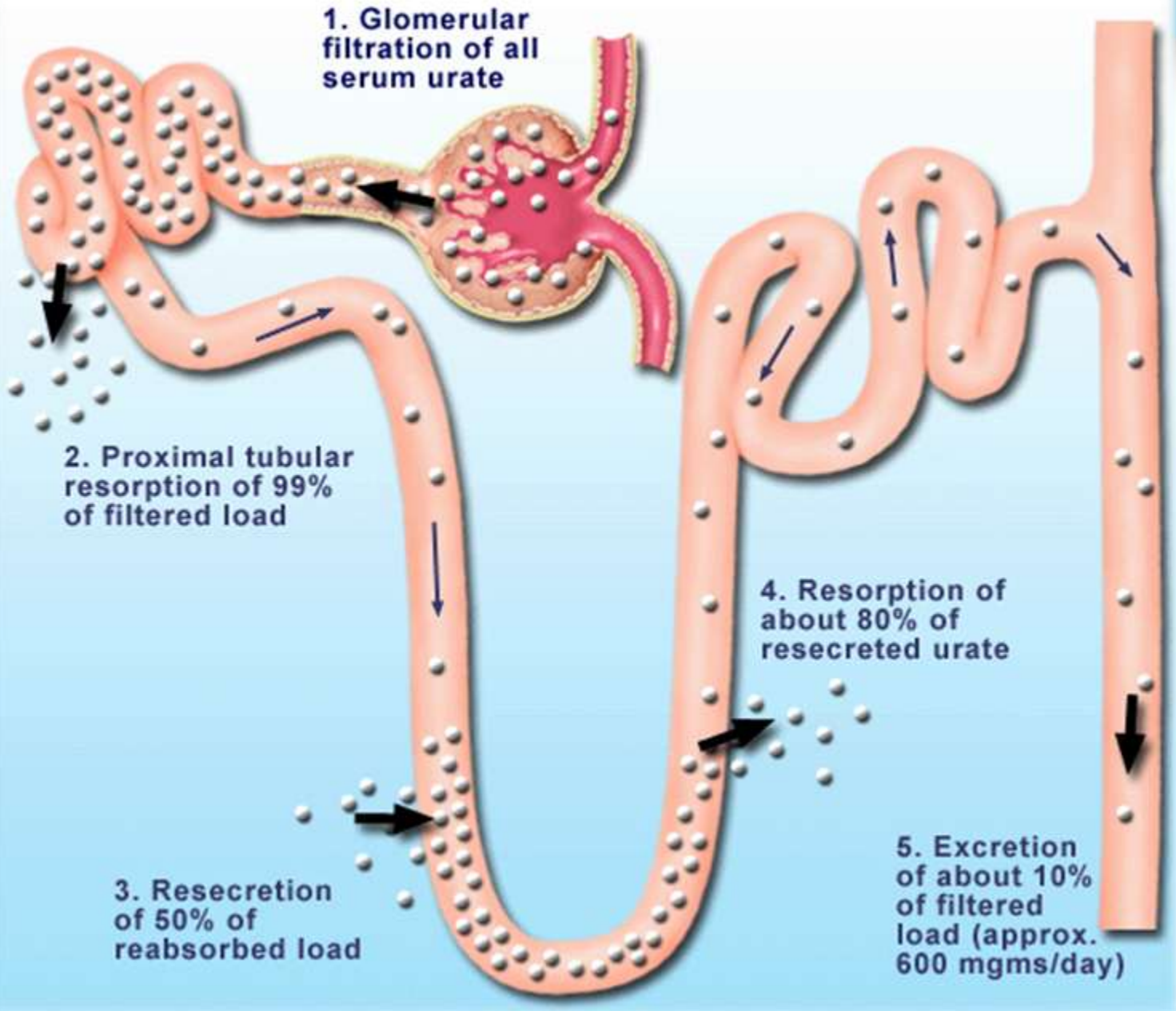
Liver

Uric Acid Pool

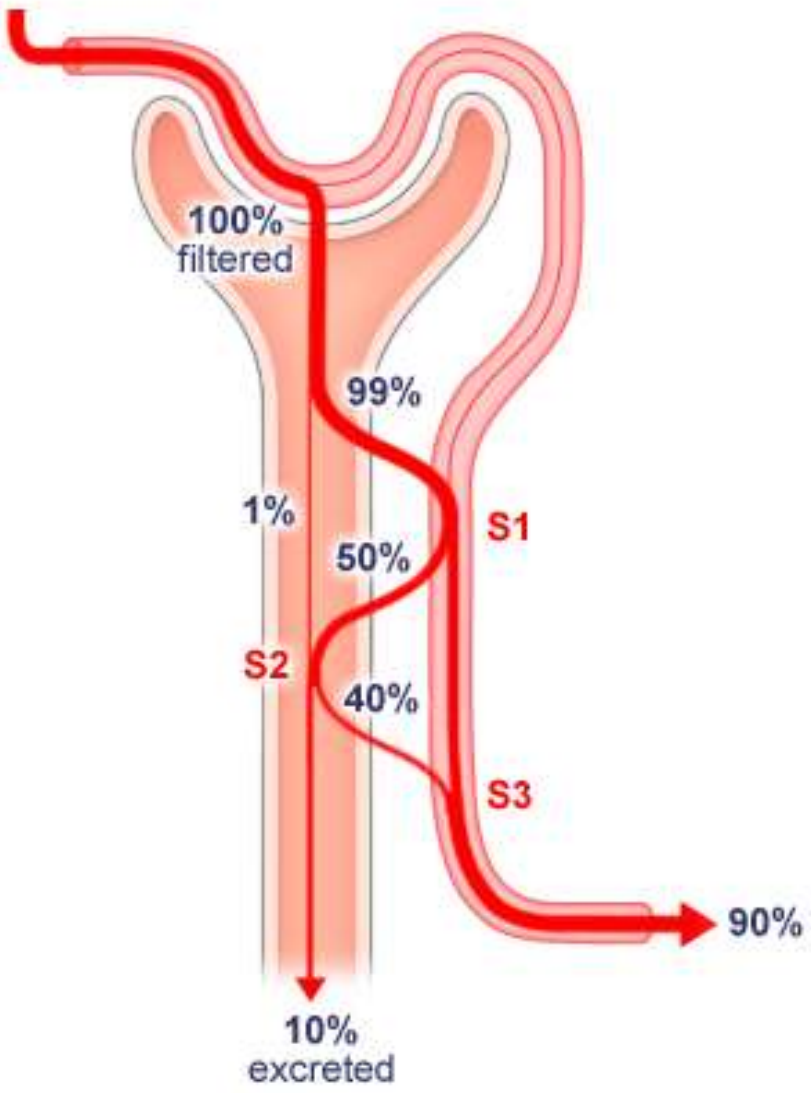
Intestine

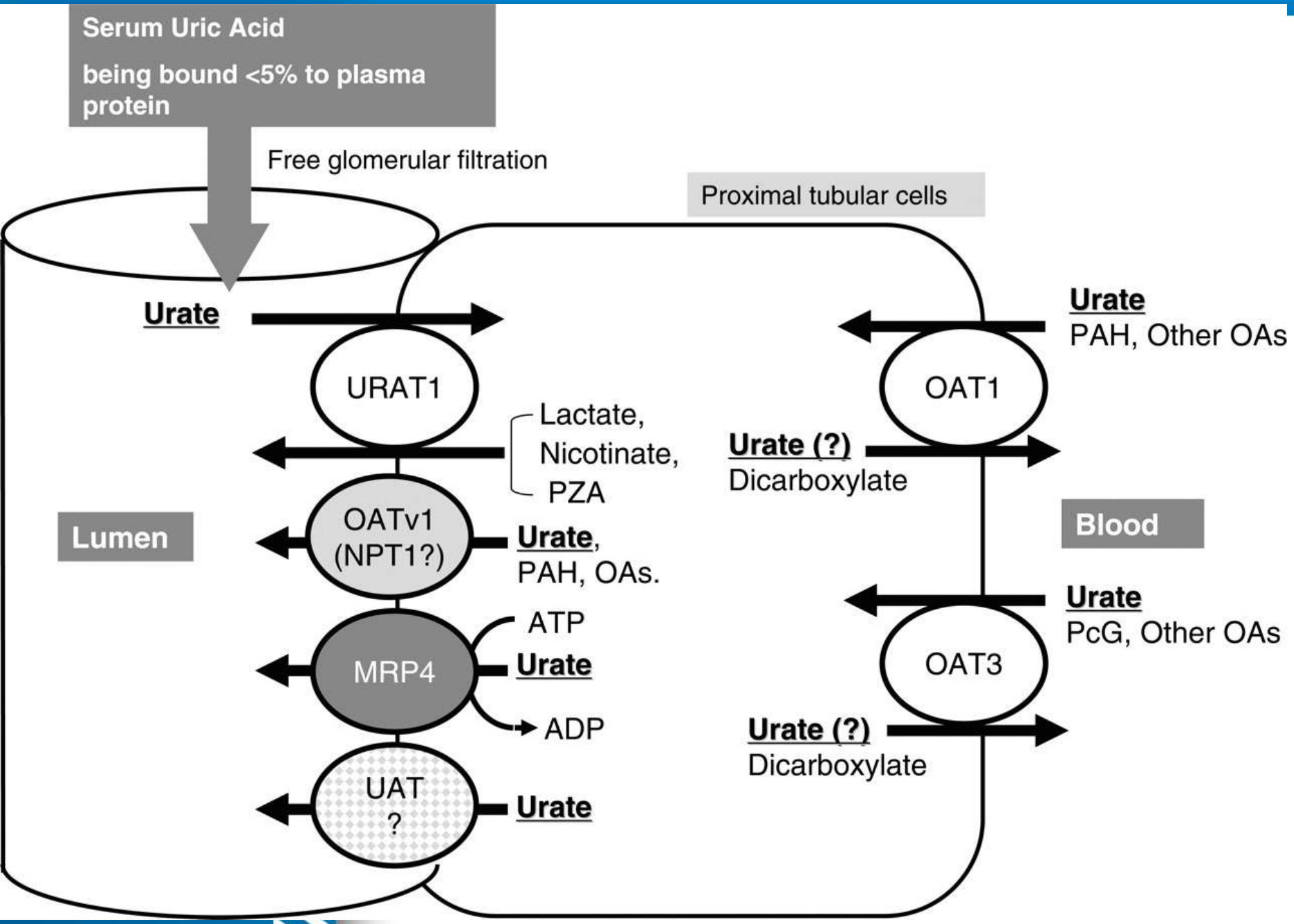
Kidney

A simplified diagram of the pathways probably involved in the excretion of Uric Acid from the Kidney



Renal Handling of Urate




Serum Uric Acid
being bound <5% to plasma protein
Free glomerular filtration
Proximal tubular cells
Urate
URAT1
Lactate,
Nicotinate,
PZA
Lumen
OATv1
(NPT1?)
Urate,
PAH, OAs.
ATP
MRP4
Urate
ADP
UAT
?
Urate
Urate
PAH, Other OAs
OAT1
Urate (?)
Dicarboxylate
Blood
Urate
PcG, Other OAs
OAT3
Urate (?)
Dicarboxylate

Hyperuricemia (>6.8 mg/dL)

Over production of uric acid

Dominant cause of hyperuricemia in ~10%

- Diet, alcohol
- High cell turnover
  - myeloproliferative disorders
  - lymphomas
  - psoriasis or Paget's disease of bone
- Identifiable genetic disorders of purine metabolism are rare, suspect these with gout onset before age 30
- Tumor lysis in chemotherapy

Underexcretion of uric acid

Dominant cause of hyperuricemia in ~ 90%

- Genetics
- CKD
- Insulin resistance
- Hypertension
- Thiazide or loop diuretics
- Low dose aspirin
- Cyclosporine A, pyrazinamide

Luk et al, Am J Manag Care 2005; 11: S435–42

Spot urine ratio of uric acid to creatinine

- A ratio greater than 0.8 indicates overproduction.
- Helps differentiate acute uric acid nephropathy from the hyperuricemia that occurs secondary to renal failure.

  The ratio is greater than 0.9 in acute uric acid nephropathy and usually less than 0.7 in hyperuricemia secondary to renal insufficiency.

The fractional excretion of urate

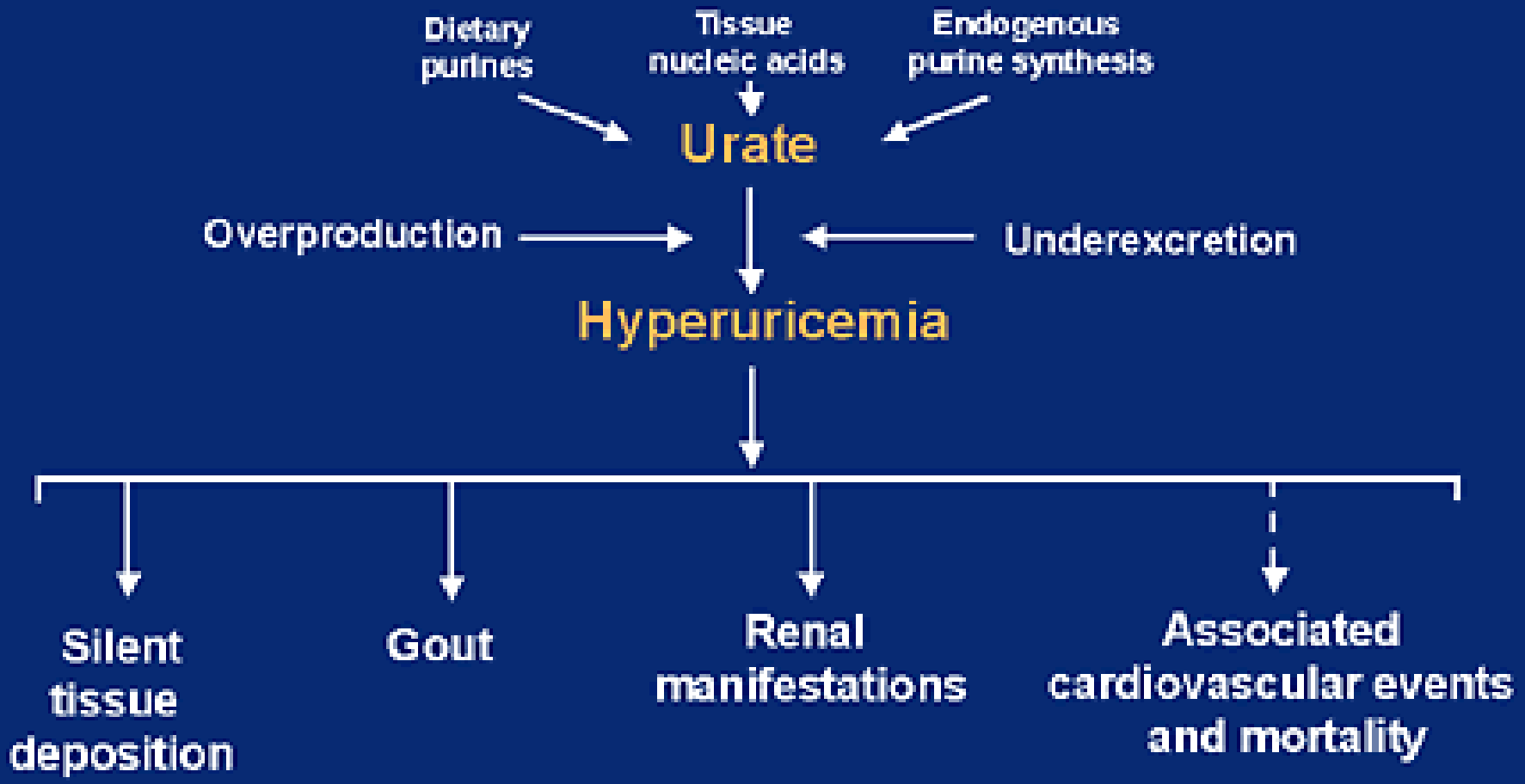
Fractional excretion of urate = [(urine uric acid)*(serum creatinine)*(100%)]/[(serum uric acid)*(urine creatinine)]

- The reference intervals for patients on a low-purine diet and normal renal function are as follows:
  - Males - 7-9.5%
  - Females - 10-14%

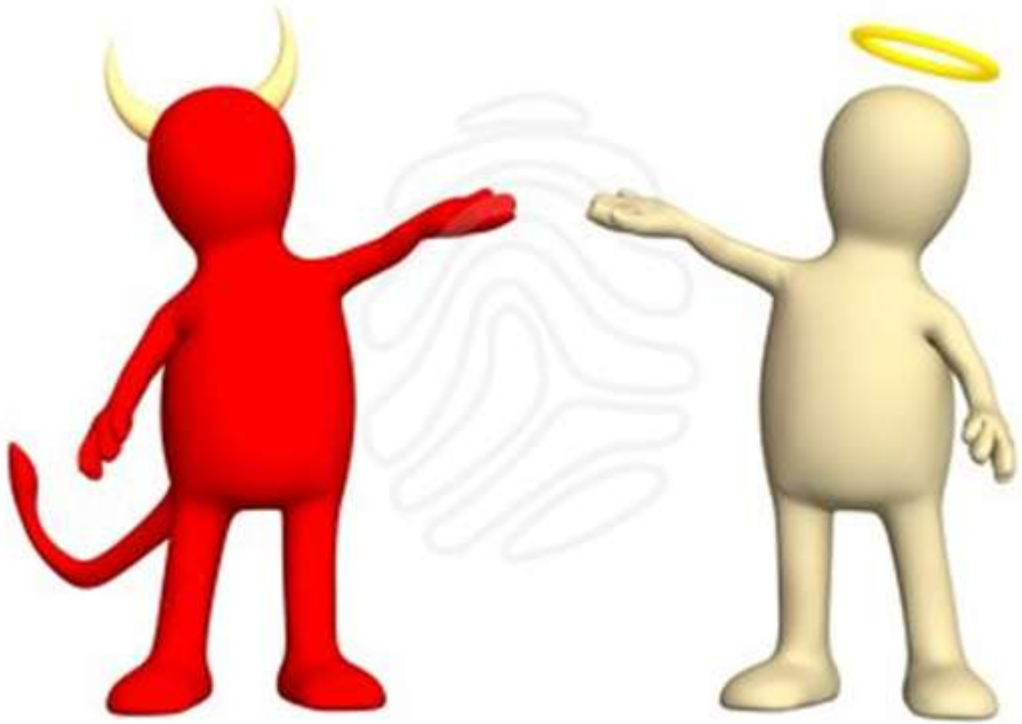
The fractional excretion of urate

- Underexcretion is defined as a fractional excretion of uric acid below 6 percent.

The Hyperuricemia Cascade



URIC ACID



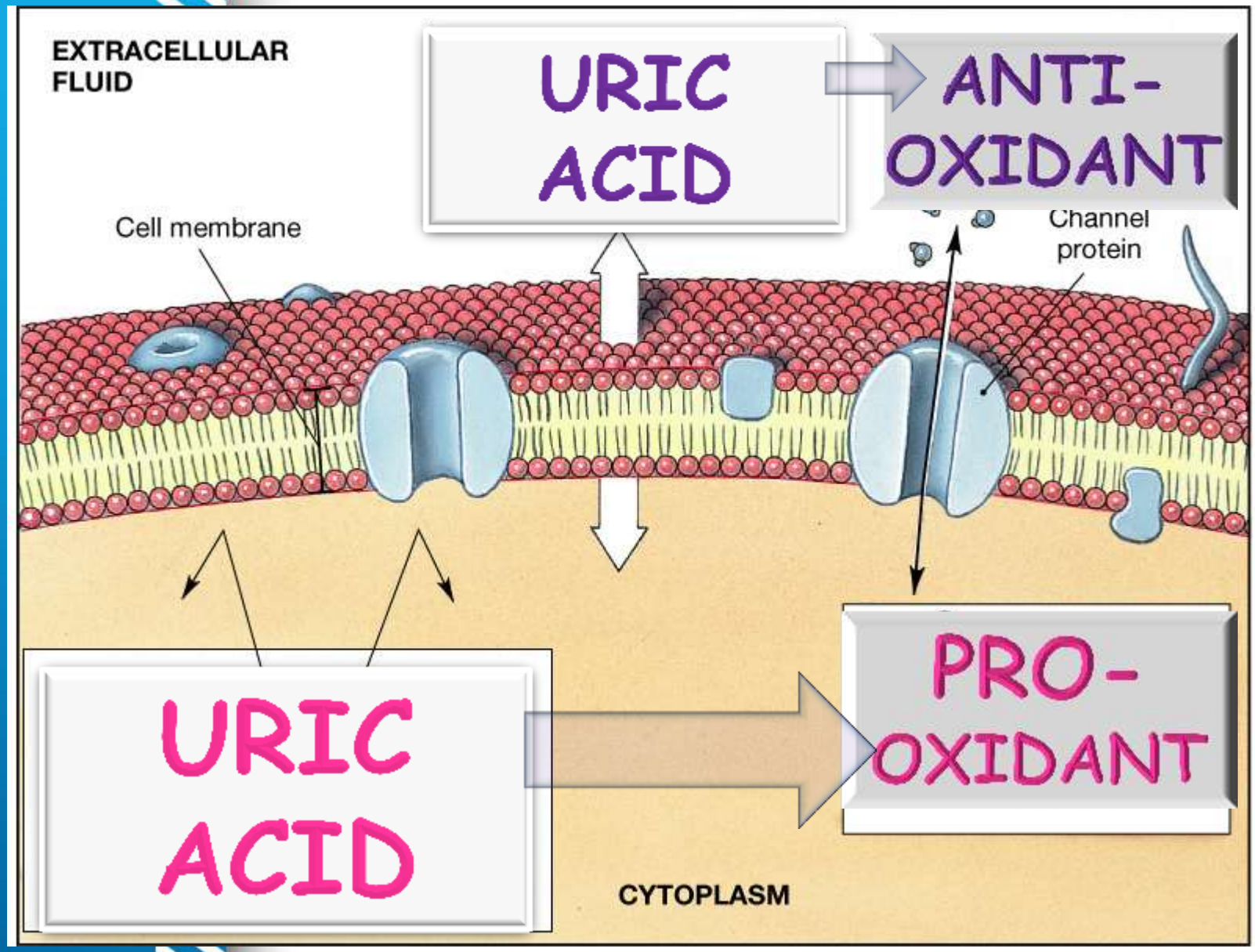
EVIL OR ANGEL

URIC ACID

ASYMPTOMATIC

BENEFICIAL

DELETERIOUS


EXTRACELLULAR FLUID
URIC ACID
ANTI-OXIDANT
Cell membrane
Channel protein
URIC ACID
PRO-OXIDANT
CYTOPLASM

Nephrol Dial Transplant (2013) 28: 2221–2228
doi: 10.1093/ndt/gft029
Advance Access publication 29 March 2013

ndt
Nephrology Dialysis Transplantation

Full Reviews

Uric acid and chronic kidney disease: which is chasing which?

Richard J. Johnson[1],
Takahiko Nakagawa[2],
Diana Jalal[1],
Laura Gabriela Sánchez-Lozada[3],
Duk-Hee Kang[4]
and Eberhard Ritz[5]

[1]Division of Kidney Diseases and Hypertension, University of Colorado Denver, Aurora, CO, USA,
[2]TMK project, Medical Innovation Center, Kyoto University, Kyoto, Japan,
[3]Laboratory of Renal Physiopathology INC Ignacio Chavez, Mexico City, DF, Mexico,
[4]The Division of Nephrology, Department of Internal Medicine, Ewha Womans University School of Medicine, Ewha Medical Research Center, Seoul, Korea and
[5]Department of Nephrology, Klinikum der Universität, Heidelberg, Germany

BENEFICIAL EFFECTS OF

URIC ACID

- ANTI-OXIDANT
- MAINTAIN BP
- ARREST MS

OXFORD JOURNALS

QJM

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CU

Oxford Journals › Medicine › QJM: An International Journal of Medicine › Volume 104, Iss

Is there anything good in uric acid?

B. Álvarez-Lario[1] and J. MacArrón-Vicente[2]

+ Author Affiliations

Diet and nucleotide turnover

↓

Inosine

↓

Hypoxanthine

↓

Xanthine

↓ Xanthine oxidase

Allantoin ← Uricase — Urate → Excretory mechanisms

Normal serum level
Human: 4–6 mg/dl (240–360 μM)
Mouse: <1 mg/dl (60 μM)

Urinary: 80%
Gastrointestinal: 20%

↓

Hyperuricemia

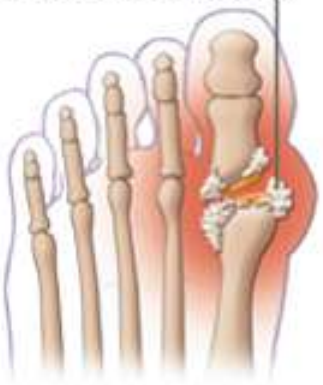
Hyperuricosuria

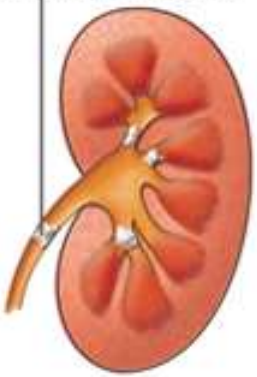
↓

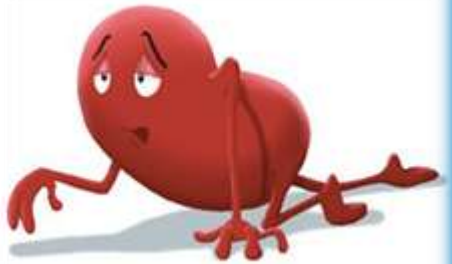
Urate crystal deposition (gout)

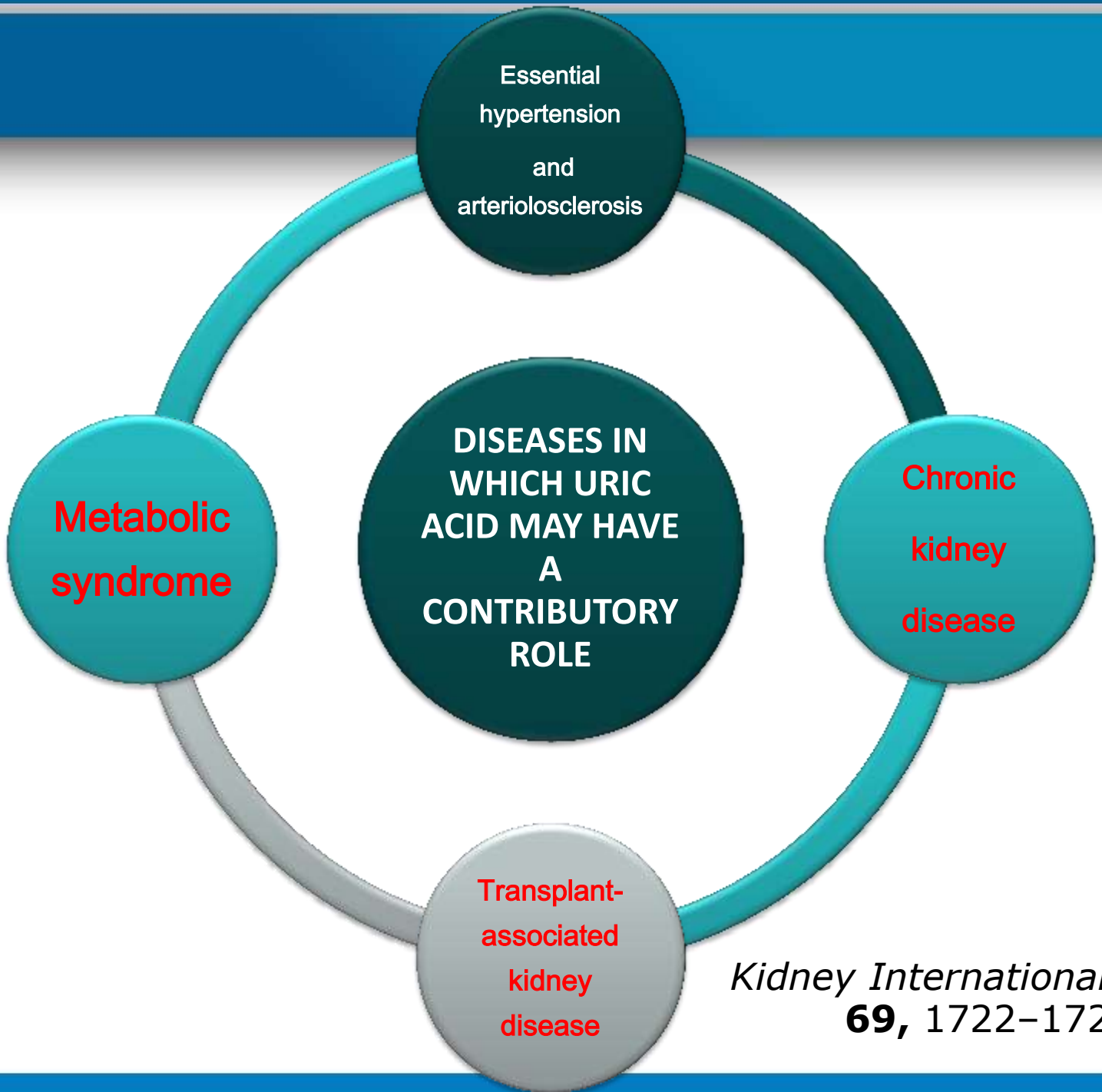
Pro-oxidant (cardiovascular effects?)

Uric acid crystals (renal calculi)









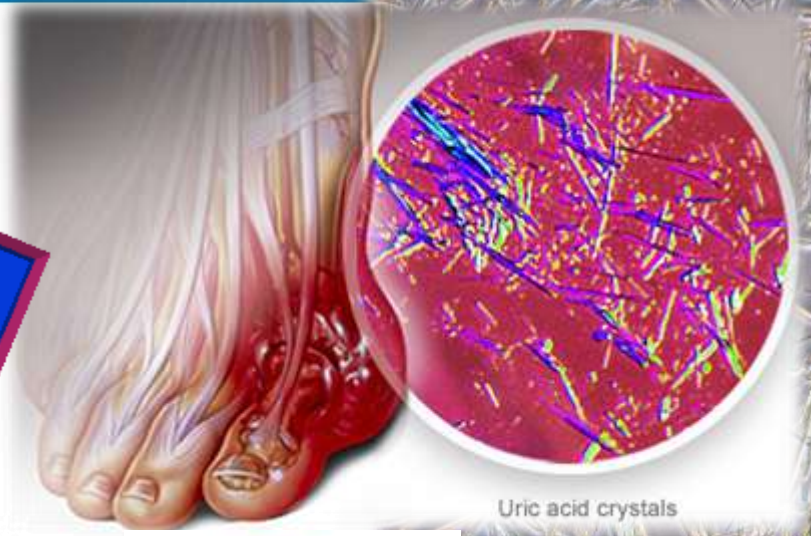
Kidney International (2006) **69,** 1722–1725.

Comorbidities Associated With Hyperuricemia

- Renal manifestations[1]
- Obesity[2]
- Metabolic syndrome[3]
- Diabetes mellitus[4]
- Heart failure[5]
- Hyperlipidemia[2]
- Hypertension[6]
- Cardiovascular disease[7]

1. Vazquez-Mellado et al. *Best Pract Res Clin Rheumatol.* 2004;18:111-124.
2. Nakanishi et al. *Int J Epidemiol.* 1999;28:888-893.
3. Ford et al. *JAMA.* 2002;287:356-359.
4. Boyko et al. *Diabetes Care.* 2000;23:1242-1248.
5. Anker et al. *Circulation.* 2003;107:1991-1997.
6. Gavin et al. *Am J Cardiovasc Drugs.* 2003;3:309-314.
7. Niskanen et al. *Arch Intern Med.* 2004;164:1546-1551

URIC ACID



Mild elevation of uric acid level in intra/extracellular condition

Mechanisms

- RAS activation
- Oxidative stress due to NADPH oxidase activation
- Mitochondrial dysfunction
- Epithelial-mesenchymal transition
- Endothelial dysfunction
- Vascular smooth muscle cell proliferation
- Others

Renal phenotype

- Arteriolosclerosis
- Glomerular hypertension
- Glomerulosclerosis
- Interstitial disease
- Acute kidney Injury

Non-renal phenotype

- Metabolic syndrome
- Non-alcoholic fatty liver disease
- Hypertension
- Diabetes

URIC ACID

U.A.STONES

ACUTE URATE NEPHROPATHY

CKD

URIC ACID

INITIATOR

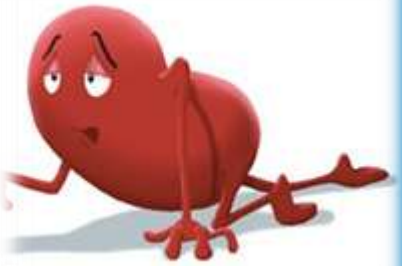
PROGRESSOR

BOTH

CKD

Summary of Risk Factors Associated with the Initiation and Progression of CKD

Initiation Factors	Progression Factors
Systemic hypertension	Older age
Diabetes mellitus	Gender (male)
Cardiovascular disease	Race/ethnicity
Dyslipidemia	Genetic predisposition
Obesity/metabolic syndrome	Poor blood pressure control
Hyperuricemia	Poor glycemia control
Smoking	Proteinuria
Low socioeconomic status	Cardiovascular disease
Nephrotoxins exposure: NSAIDs, analgesics, traditional herbal use, heavy metals exposure (such as lead)	Dyslipidemia Smoking Obesity/metabolic syndrome Hyperuricemia Low socioeconomic status Alcohol consumption Nephrotoxins; NSAIDs, RCM, herbal remedies Acute kidney injury



The Journal of Rheumatology

The Journal of Rheumatology Volume 40, no. 7

Serum Urate and Incidence of Kidney Disease Among Veterans with Gout

Eswar Krishnan, Kasem S. Akhras, Hari Sharma, Maryna Marynchenko, Eric Wu, Rima H. Tawk, Jinan Liu and Lizheng Shi

J Rheumatol 2013;40;1166-1172

Conclusion: Male veterans with gout and sUA levels > 7 mg/dl had an increased incidence of kidney disease.

Table 1: An elevated serum uric acid predicts the development of CKD

Location	Population	Follow-up (years)	Type	Indep?	Author (year)
Japan	6403 adults	2	CKD	Yes	Iseki (2001)
Japan	48 177 adults	10	ESRD	Women	Iseki (2004)
Thailand	3499 adults	12	CKD	Yes	Domrongkitchaiporn (2005)
USA	5808 adults	5	CKD	No	Chonchol (2007)
Austria	21 457 adults	7	CKD	Yes	Obermayr (2008)
USA	13 338 adults	8.5	CKD	Yes	Weiner (2008)
Austria	17 375 adults	7	CKD	Yes	Obermayr (2008)
USA	177 500 adults	25	ESRD	Yes	Hsu (2009)
USA	355 type 1 diabetes[a]	6	CKD	Yes	Ficociello (2010)
Italy	900 adults	5	CKD	Yes	Bellomo (2010)
Japan	7078 adults	5	CKD	Yes	Sonoda (2011)
Taiwan	94 422 adults	3.5	CKD	Men	Wang (2011)
Israel	2449 adults	26	ESRD	Yes	Ben-Dov (2011)
Japan	14 399 adults	5	CKD	Yes	Yamada (2011)
USA	488 renal transplants	1	Graft Loss	Yes	Haririan (2011)
China	1410 adults	4	CKD	Yes	Zhang (2012)
Korea	14 939 adults	10.2	CKD	Men	Mok (2012)

American Diabetes Association. Diabetes Care

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Serum Uric Acid Levels and Incident Chronic Kidney Disease in Patients With Type 2 Diabetes and Preserved Kidney Function

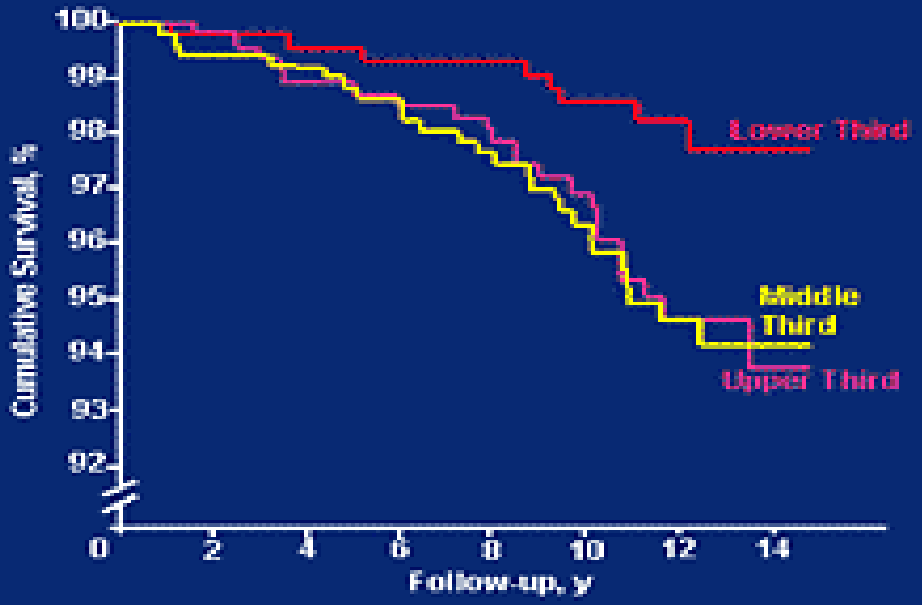
Diabetes Care January 2012 vol. 35no. 1 99-104

Giacomo Zoppini, MD[1], Giovanni Targher, MD[1], Michel Chonchol, MD[2], Vittorio Ortalda, MD[3], Cataldo Abaterusso, MD[3], Isabella Pichiri, MD[1], Carlo Negri, MD[1] and Enzo Bonora, MD[1]

CONCLUSIONS In type 2 diabetic individuals with preserved kidney function, hyperuricemia seems to be an independent risk factor for the development of incident CKD.

Higher Cardiovascular Mortality Associated With Higher Serum Urate

Prospective study done in 1423 healthy, middle-aged men

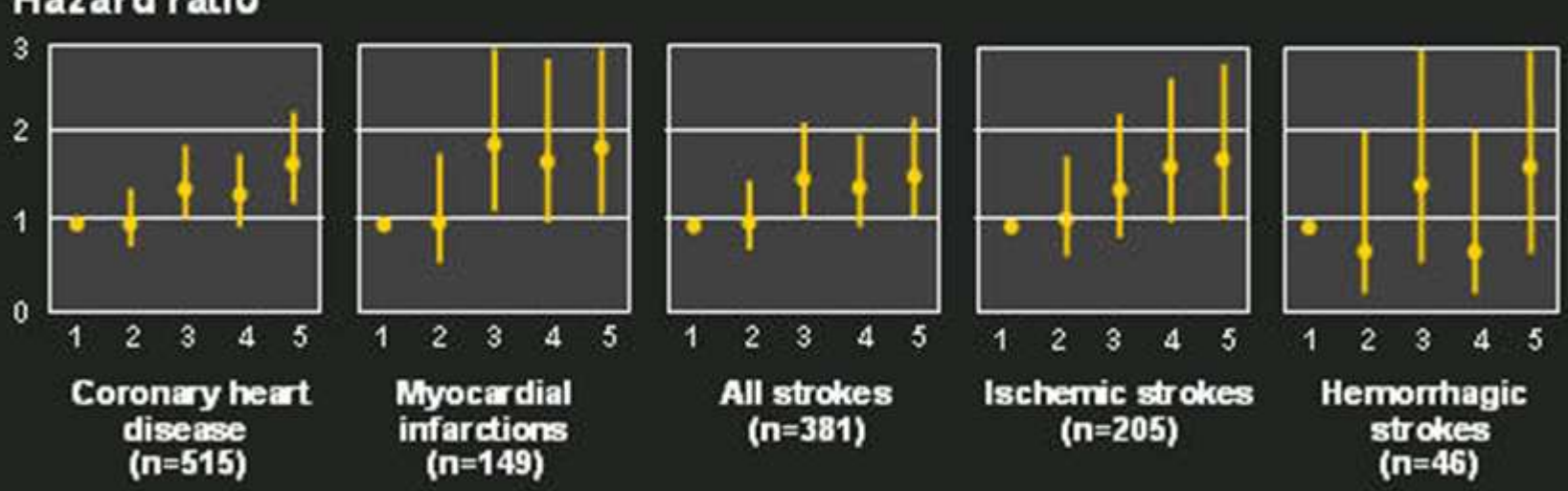


- Men divided into 3 groups according to serum urate levels
  - Lower third: 3.03-5.04 mg/dL
  - Middle third: 5.05-5.88 mg/dL
  - Upper third: 5.89-9.58 mg/dL

Niskanen et al. *Arch Intern Med.* 2004;164:1546-1551.

Uric acid as a factor for MI and stroke (The Rotterdam Study)

- 4,385 participants aged ≥55 years; average follow-up 8.4 years
  Total of 36,794 person-years



- High serum urate levels were associated with risk of MI and stroke
- Serum urate is a strong risk factor for myocardial infarction and stroke

Bos et al, Stroke 2006; 37: 1503–7

Review Q J Med 2000; 93:707–713 QJM

Uric acid as a risk factor for cardiovascular disease

W.S. WARING, D.J. WEBB and S.R.J. MAXWELL

From the Clinical Pharmacology Unit and Research Centre, Department of Medical Sciences, University of Edinburgh, Edinburgh, UK

Serum Uric Acid Levels Correlate with the Severity and the Mortality of Primary Pulmonary Hypertension

NORITOSHI NAGAYA, MASAAKI UEMATSU, TORU SATOH, SHINGO KYOTANI, FUMIO SAKAMAKI, NORIFUMI NAKANISHI, MASAKAZU YAMAGISHI, TAKEYOSHI KUNIEDA, and KUNIO MIYATAKE

Division of Cardiology, Department of Medicine, National Cardiovascular Center, Osaka; Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Osaka; and Department of Medicine, Ise Keio Hospital, Keio University, Mie, Japan

AMERICAN JOURNAL OF HYPERTENSION

ABOUT THIS JOURNAL CONTACT THIS JOURNAL SUBSCRIPTIONS CURRE

Oxford Journals › Medicine › American Journal of Hypertension › Volume 26, Issue 2 › Pp. 243

Association of Uric Acid and Left Ventricular Mass Index With Renal Outcomes in Chronic Kidney Disease

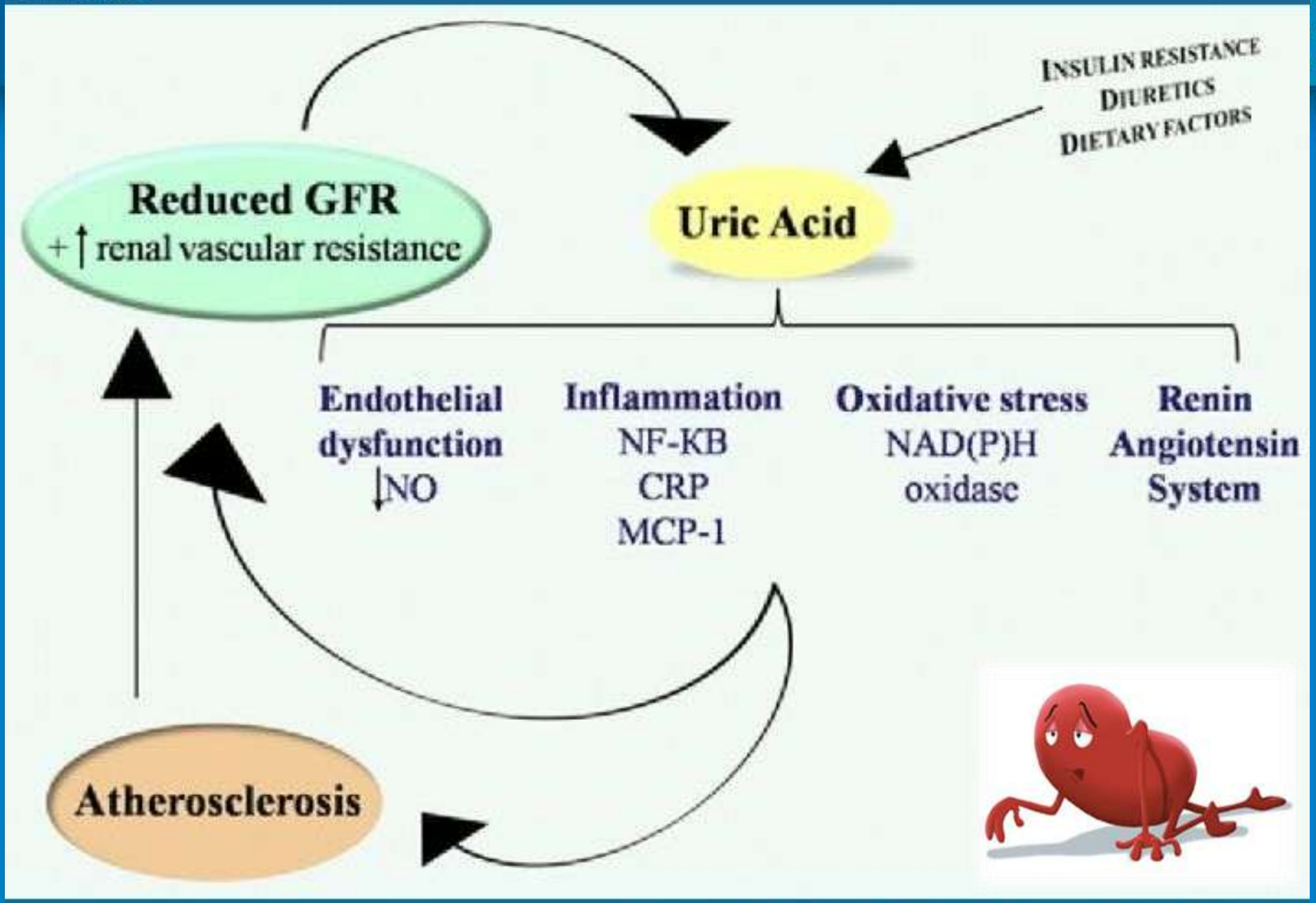
Szu-Chia Chen[1,3,5], Jer-Ming Chang[1,3,4], Shin-Meng Yeh[1], Ho-Ming Su[2,3,5] and Hung-Chun Chen[1,4]

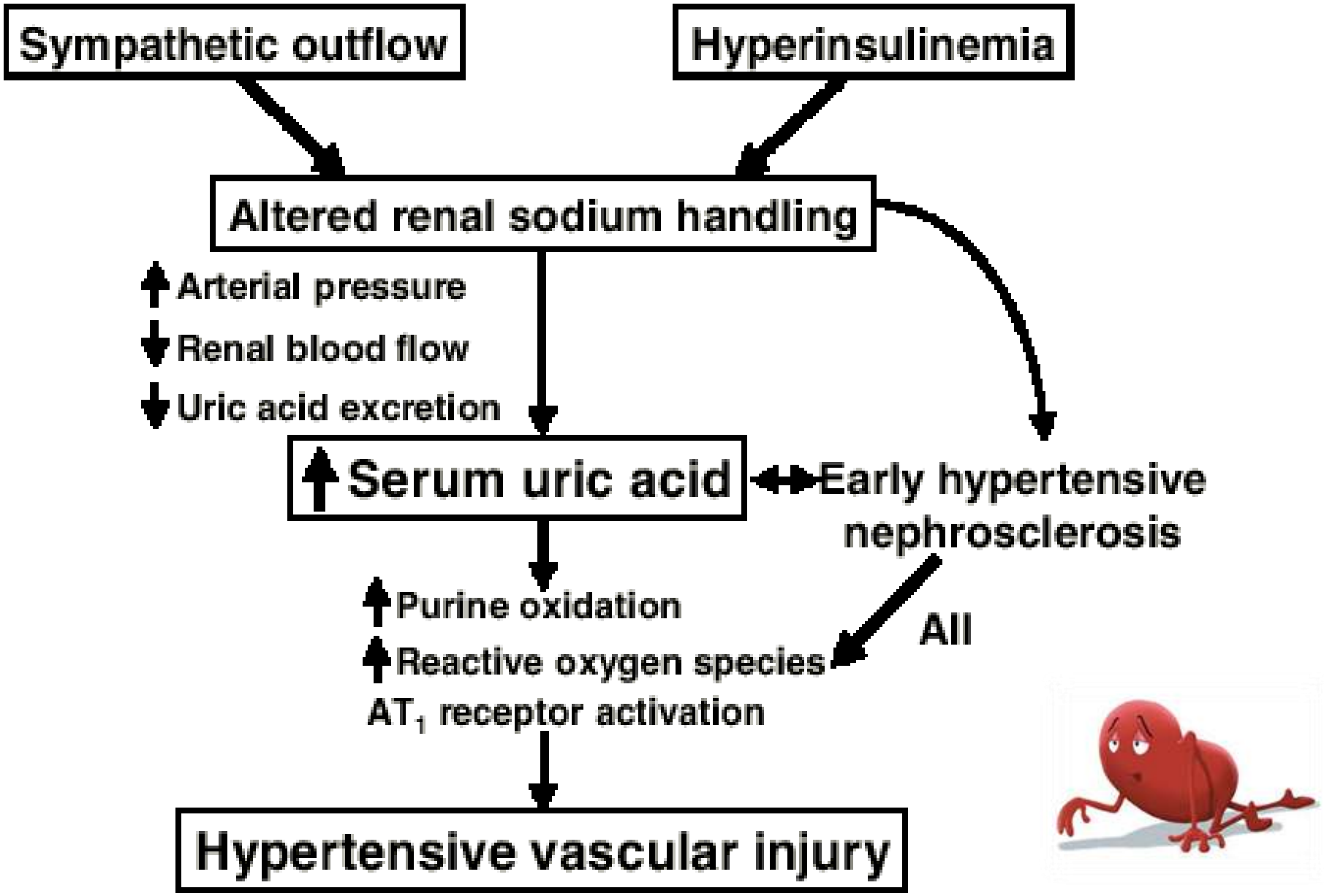
+ Author Affiliations

Correspondence Ho-Ming Su, (cobeshm@seed.net.tw).

Received May 6, 2012.
Revision received September 6, 2012.
Accepted September 15, 2012.

CONCLUSIONS Our findings show that the combination of a higher UA and LVMI is a risk factor for progression to dialysis and rapid progression of decline in renal function in patients with CKD of stages 3–5.





PATHOGENICALLY RELATED

Chronic kidney disease → ↑ Uric acid

Underlying condition → ↑ Uric acid

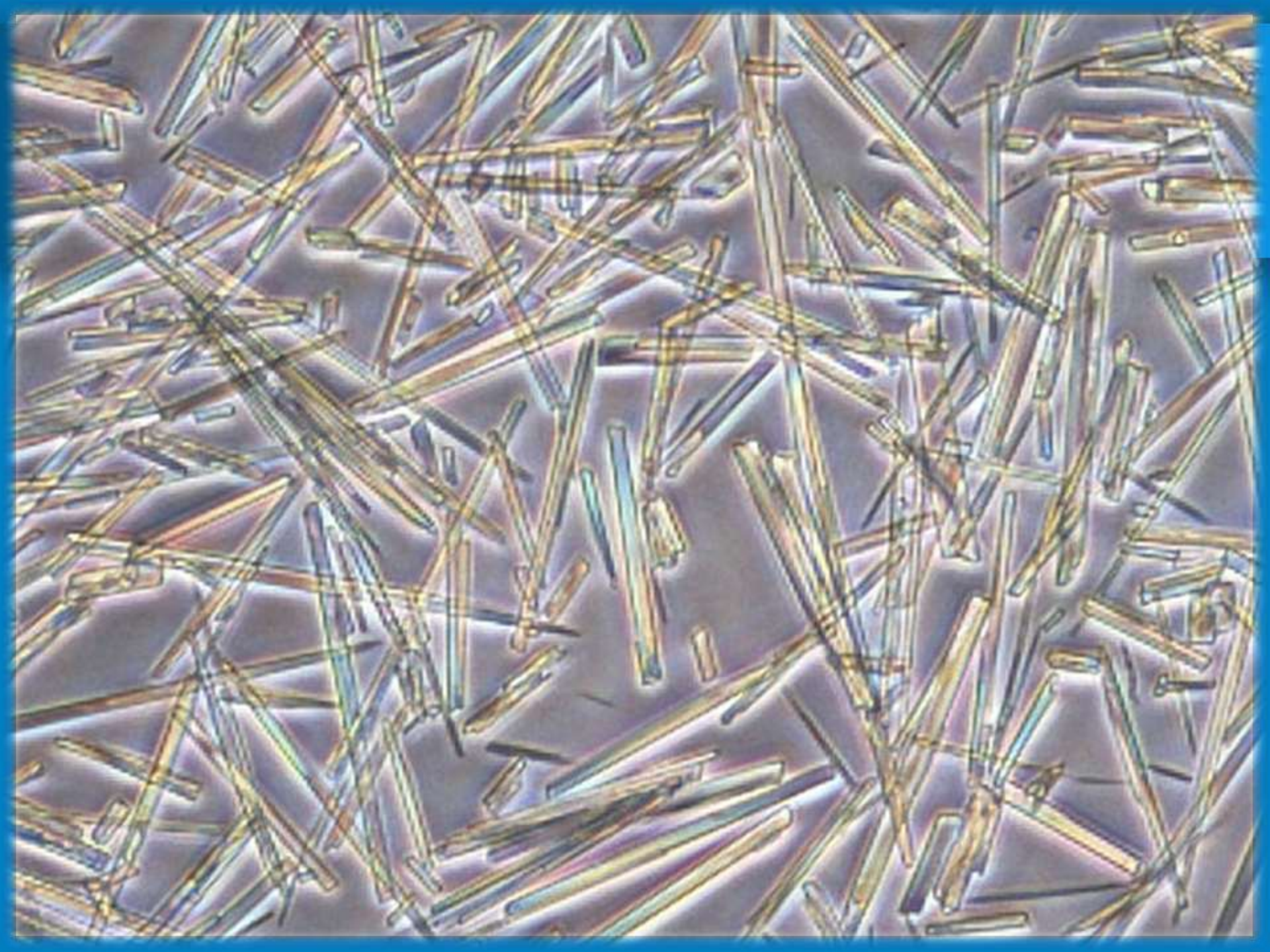
Underlying condition → Chronic kidney disease

↑ Uric acid → * → Chronic kidney disease

UNRELATED COEXISTENCE

↑ Uric acid

Chronic kidney disease



Gouty Nephropathy.

Gout was considered a cause of CKD in the mid-nineteenth Century.
During life impaired renal function occurred in half of these subjects.

Gout was removed from the textbooks as a cause of CKD.

WHY...?

- The common association of hyperuricemia with CKD was solely attributed to the retention of serum uric acid that is known to occur as the glomerularfiltration rate falls.

- Many subjects with gout also had coexistent conditions such as hypertension and vascular disease.

- The presence of uric acid crystals in the kidney may occur in subjects without renal disease; furthermore, the focal location of the crystals could not explain the diffuse renal scarring present.

increased uric acid

Uric acid causes hypertension

kidney disease

hypertension

hypertension

kidney disease

Uric acid is associated but doesn't cause hypertension

increased uric acid

Elevation OF serum urate concentration in proportion to the degree of renal insufficiency

S.Creatinine	Expected S.Uric acid
≤1.5 mg/dL	Greater than 9 mg/dL
Between 1.5 and 2 mg/dL	Greater than 10 mg/dL
>2 mg/dL	Greater than 12 mg/dL

Asymptomatic hyperuricemia: To treat or not to treat

CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 69 • NUMBER 8 AUGUST 2002

- Persistent hyperuricemia in the infrequent patients with sustained serum urate concentrations greater than 13 mg/dL in men and 10 mg/dL in women.
- Excretion of urinary uric acid in excess of 1100 mg daily

THERAPY OF HYPERURICEMIA

Purine content of foods

Purine-rich foods
- Anchovies
- Consomme
- Legumes
- Meat extracts
- Organ meats (brains, kidneys, liver, sweetbreads)
- Roe (fish eggs)
- Sardines
- Yeast

Moderate-purine foods
- Asparagus
- Fish
- Meat
- Mushrooms
- Peas (dried)
- Shellfish
- Spinach

Low-purine foods
- Bread and butter
- Cereals
- Cheese
- Chocolate
- Coffee
- Eggs
- Fruit
- Milk
- Noodles
- Nuts
- Olives
- Rice
- Salt

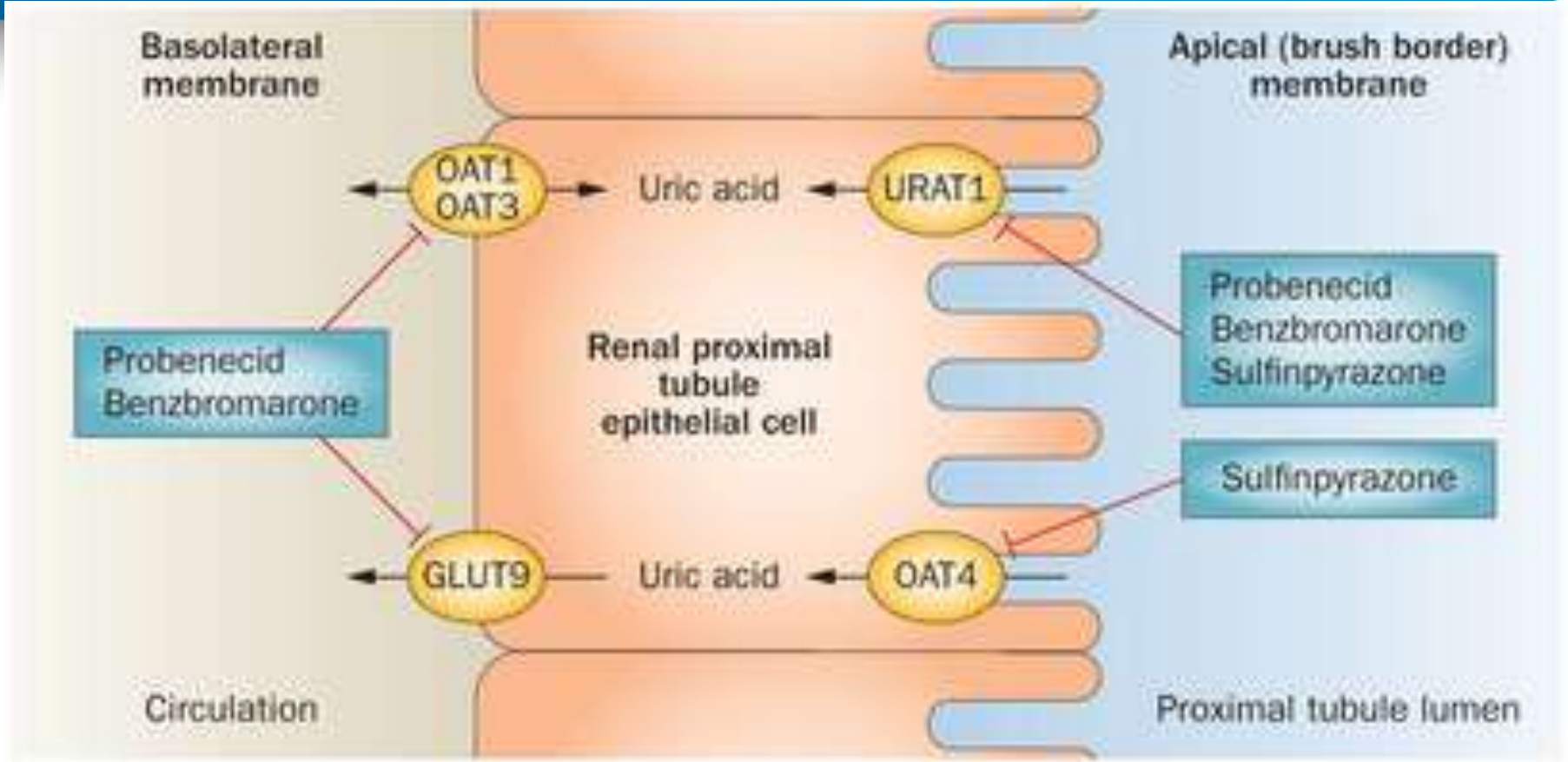
CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 69 • NUMBER 8 AUGUST 2002

(Purines in milligrams per 100 grams)

Meats & Fishes		Beans & Legumes		Vegetables/Fruits	
Chicken	175	Mung Beans	222	Raisins	107
Veal	172	Soy Beans	190	Broccoli	81
Salmon	170	White Beans	128	Artichoke	78
Pork	166	Lentils	127	Leek	74
Turkey	150	Garbanzo	109	Apricot	73
Shrimp	147	Green Peas	84	Brussels	69
Duck	138	Bean Sprout	80	Dried Plum	64
Venison	138	Tofu	68	Mushroom	58
Scallops	136	French Beans	45	Banana	57
Beef	133	String Beans	37	Spinach	57
Rabbit	132			Corn	52
Lobster	118			Cauliflower	51
Mussels	112			Cabbage	37
Cod	109			Grapes	27
Oysters	90			Asparagus	23

Table 3. Pharmacologic Treatment Options for the Management of Hyperuricemia

Class	Drug (Brand)	Common Dosing
		Urate-Lowering Therapy
Xanthine oxidase inhibitors	Allopurinol (Zyloprim)	*Starting dose:* 100 mg/day (all patients); 50 mg/day (stage 4 CKD or worse) *Dose titration:* Titrate to doses >300 mg/day even in renal patients; doses >300 mg/day may be required for most patients. Max daily dose is 800 mg
	Febuxostat (Uloric)	*Starting dose:* 40 mg/day *Dose titration:* Increase to 80 mg/day after 2-4 wk
Uricosuric agents	Probenecid (Benemid)	*Starting dose:* 250 mg/day *Dose titration:* Increase by 500 mg per month to a max dose of 2-3 g/day (2 divided doses) in patients with normal renal function
Uricase agents	Pegloticase (Krystexxa)	*Dose:* IV infusion 8 mg every 2 wk


Basolateral membrane
Apical (brush border) membrane
OAT1
OAT3
Uric acid
URAT1
Probenecid
Benzbromarone
Sulfinpyrazone
Renal proximal tubule epithelial cell
Probenecid
Benzbromarone
Sulfinpyrazone
GLUT9
Uric acid
OAT4
Circulation
Proximal tubule lumen

Medications with Uricosuric Activity

- Acetohexamide
- ACTH
- Ascorbic acid
- Azauridine
- Benzbromarone
- Calcitonin
- Chlorprothixene
- Citrate
- Dicumarol
- Diflunisal
- Estrogens
- Fenofibrate
- Glucocorticoids
- Glyceryl guaiacolate
- Glycopyrrolate
- Halofenate
- Losartan
- Meclofenamate
- Phenolsulfonphthalein
- Phenylbutazone
- Probenecid
- Radiographic contrast agents
- Salicylates (>2 g/2d)
- Sulfinpyrazone
- Tetracycline that is outdated
- Zoxazolamine

CJASN ePress. Published on June 10, 2010 as doi: 10.2215/CJN.01580210

Effect of Allopurinol in Chronic Kidney Disease Progression and Cardiovascular Risk

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Background and objectives: Hyperuricemia is associated with hypertension, inflammation, renal disease progression, and cardiovascular disease. However, no data are available regarding the effect of allopurinol in patients with chronic kidney disease.

Design, setting, participants, & measurements: We conducted a prospective, randomized trial of 113 patients with estimated GFR (eGFR) <60 ml/min. Patients were randomly assigned to treatment with allopurinol 100 mg/d ($n = 57$) or to continue the usual therapy ($n = 56$). Clinical, biochemical, and inflammatory parameters were measured at baseline and at 6, 12, and 24 months of treatment. The objectives of study were: (1) renal disease progression; (2) cardiovascular events; and (3) hospitalizations of any causes.

Results: Serum uric acid and C-reactive protein levels were significantly decreased in subjects treated with allopurinol. In the control group, eGFR decreased 3.3 ± 1.2 ml/min per 1.73 m^2, and in the allopurinol group, eGFR increased 1.3 ± 1.3 ml/min per 1.73 m^2 after 24 months. Allopurinol treatment slowed down renal disease progression independently of age, gender, diabetes, C-reactive protein, albuminuria, and renin-angiotensin system blockers use. After a mean follow-up time of 23.4 ± 7.8 months, 22 patients suffered a cardiovascular event. Diabetes mellitus, previous coronary heart disease, and C-reactive protein levels increased cardiovascular risk. Allopurinol treatment reduces risk of cardiovascular events in 71% compared with standard therapy.

Conclusions: Allopurinol decreases C-reactive protein and slows down the progression of renal disease in patients with chronic kidney disease. In addition, allopurinol reduces cardiovascular and hospitalization risk in these subjects.

Clin J Am Soc Nephrol 5: ●●●–●●●, 2010. doi: 10.2215/CJN.01580210

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Safety and Efficacy of Allopurinol in Chronic Kidney Disease

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Conclusions: Studies evaluating allopurinol use in patients with CKD have reported inconsistent findings relative to safety and efficacy. Providers should be aware of the potential risk of allopurinol hypersensitivity syndrome as well as the need for reducing the initiation dose and gradual titration of allopurinol to safely achieve a target serum urate level in this population.

Ren Fail. 2014 Mar;36(2):225-31. doi: 10.3109/0886022X.2013.844622. Epub 2013 Oct 24.

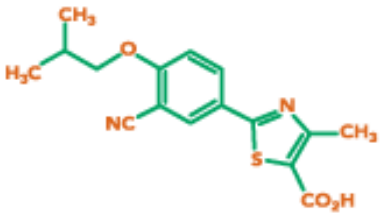
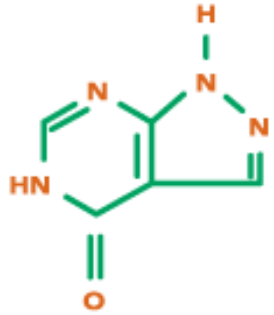
Febuxostat for treating allopurinol-resistant hyperuricemia in patients with chronic kidney disease.

Sakai Y[1], Otsuka T, Ohno D, Murasawa T, Sato N, Tsuruoka S.

Author information

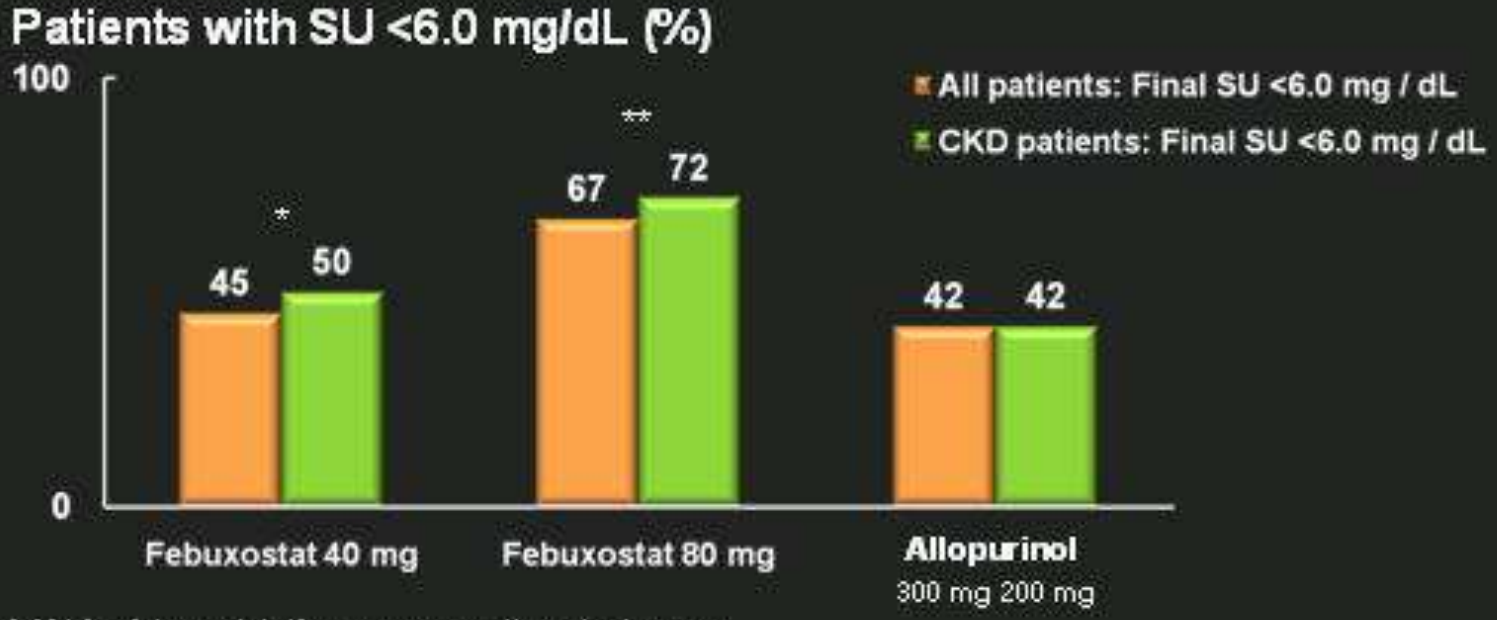
Abstract

Abstract Background: Availability of the novel xanthine oxidase inhibitor febuxostat, which has multiple excretion pathways, enables investigation of the significance of serum uric acid control on renal function in patients with chronic kidney disease (CKD). Methods: This was an exploratory, retrospective, observational study conducted at a single Japanese center. Serum uric acid concentrations and serum creatinine levels in the 6 months before and after the start of febuxostat treatment were collected for CKD patients switched from allopurinol after failing to achieve serum uric acid concentrations ≤6.0 mg/dL. Results: Evaluable data were available for 60 patients, 67% of whom had advanced CKD (eGFR <30 mL/min/1.73 m(2)). Mean dose of febuxostat was 15.9 (± 8) mg/day. Mean serum uric acid concentration decreased from 8.4 (±1.4) mg/dL at baseline to 6.2 (±1.2) mg/dL at 6 months; 47.5% of patients achieved a level ≤6.0 mg/dL. The change from baseline in eGFR was positive at all time points during febuxostat treatment and the increase of 2.3 (±5.6) mL/min/1.73 m(2) at 6 months was significant ($p = 0.0027$). Whereas the eGFR slope was negative during allopurinol treatment, it became positive after the switch to febuxostat. The change in eGFR slope before and after febuxostat treatment was significant for all patients ($p < 0.01$), for male patients ($p < 0.05$), and for patients with a baseline eGFR of <15 mL/min/1.73 m(2) ($p < 0.05$). Conclusions: In patients with CKD, febuxostat reduces serum uric acid concentrations effectively and may suppress the progressive decline in renal function.

	DRUG ELIMINATION	DOSING/ADMINISTRATION	
ULORIC (febuxostat)[25]			
Non-purine structure 	Both hepatic and renal elimination	1 pill daily Only one step required to achieve the maximum recommended dosage No dose adjustments in patienst with mild to moderate renal or hepatic impairment‡	Can be administered without regard to food No adjustments in patients receiving warfarin or hydrochlorothiazide ULORIC is contraindicated in patients being treated with azathioprine or mercaptopurine
ALLOPURINOL[26]			
Purine structure 	Eliminated primarily via renal excretion	Up to 4 pills May require a multisteptitration process Dose reductions mandatory in patients with renal impairment	Generally better tolerated if taken following meals Adjustments may be required in patients receiving warfarin[4] or thiazide diuretics Allopurinol is contraindicated in patients who have developed a severe reaction to allopurinol. These patients should not be restarted on the drug

CONFIRM study – Febuxostat *vs* allopurinol in patients with gout and CKD

- Randomization: FDA-approved doses of febuxostat 40 mg or 80 mg qd *vs* allopurinol 300 mg qd for 6 months
- n=2,269 (n=145 with moderate CKD on allopurinol 200 mg qd)



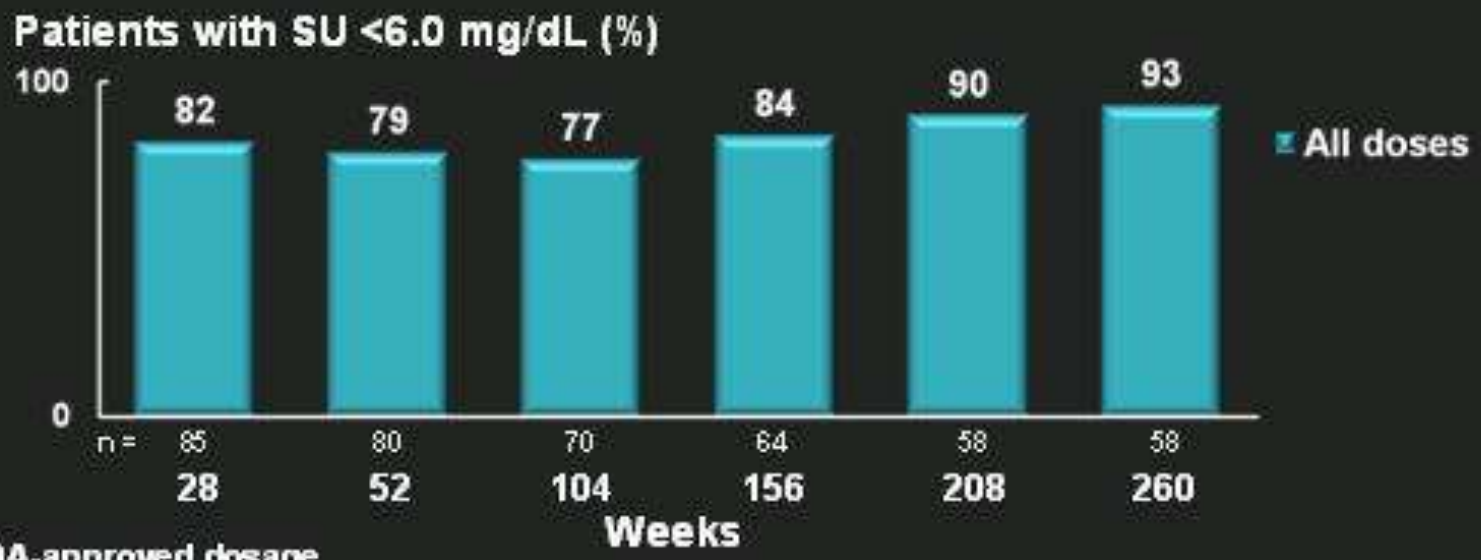
*p<0.021 for febuxostat 40 mg group *vs* allopurinol group
**p<0.001 for febuxostat 80 mg *vs* febuxostat 40 mg and allopurinol groups

Becker et al, Arthritis Rheum 2008; 58: Late breaking abstract No: L11

FOCUS study – SU <6.0 mg/dL

- 59 patients completed 260 weeks (5 years) of trial
- Dose at enrolment: Febuxostat 80 mg qd* (n=116)
- Dose adjustment in 38% patients

Febuxostat dose (mg qd)	40*	80*	120
Week 24	8	79	29
Week 260	6	41	11



*FDA-approved dosage

Schumacher et al, Rheumatology (Oxford) 2009; 48: 188–94

Study	Patients Achieving SU <6.0 mg/dL (%)			
	Febuxostat 40 mg daily	Febuxostat 80 mg daily	Allopurinol 300 mg daily	Placebo
CONFIRMS (6 months)	45 (n=757)	67*, ** (n=756)	42 (n=755)	–
APEX (6 months)	–	72 (n=253)	39*** (n=263)	1 (n=127)
FACT (12 months)	–	74 (n=249)	36 (n=242)	–

* *P*<.001 vs allopurinol

** *P*<.001 vs febuxostat 40 mg and placebo

***P*<.001 vs placebo

The possible side effects of Allopurinol

- Hypersensitivity syndrome—potentially fatal
- Fever
- Skin rash
- Hepatitis
- Worsened kidney function
- Toxic epidermal necrolysis
- Steven-Johnson syndrome
- Cytopenia
- Aplastic anemia
- Interstitial nephritis
- Peripheral neuritis, although rare
- Possible congenital defects when taken during pregnancy

Febuxostat side effects

- Nausea
- Headache
- Diarrhea
- Skin rash
- Joint pain
- An increase in the serum enzymes of the liver

Allopurinol Hypersensitivity Syndrome

- 2% of treated patients on allopurinol develop a skin rash.
- **An estimated 0.4%, particularly people with kidney failure or having concomitant thiazide diuretic therapy, may experience a severe idiosyncratic reaction, known as allopurinol hypersensitivity syndrome. This syndrome is characterised by skin reactions, fever, eosinophilia, and multiorgan involvement, with a mortality of 25%.**

Allopurinol Hypersensitivity Syndrome

Zinger JZ, Wallace SL. The allopurinol hypersensitivity syndrome. Unnecessary morbidity and mortality. Arthritis Rheum 1986;29:82–7.

Diagnostic criteria:

1. a clear history of exposure to allopurinol
2. a clinical picture consisting of either A or B, as follows:

A. at least 2 of the following major criteria:

(i) worsening renal function

(ii) acute hepatocellular injury

(iii) a rash, including either toxic epidermal necrolysis, erythema multiforme, or a diffuse maculopapular or exfoliative dermatitis

B. one of the above major criteria plus at least one of the following minor criteria:

(i) fever

(ii) eosinophilia

(iii) Leukocytosis

3. lack of exposure to another drug that might cause asimilar clinical picture.

Allopurinol SCARs

	SJS	TEN	DRESS
Mortality rate	1-5%	25-30%	10%

SCARs: severe cutaneous adverse reactions.

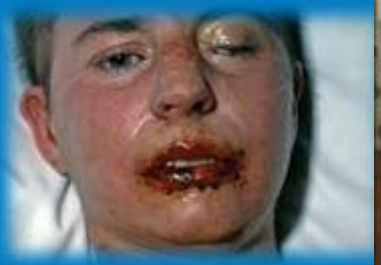
SJS: Stevens Johnson Syndrome

TEN : toxic epidermal necrolysis

DRESS: drug rash eosinophilia systemic symptoms(previously called AHS: allopurinol hypersensitivity sundrome)

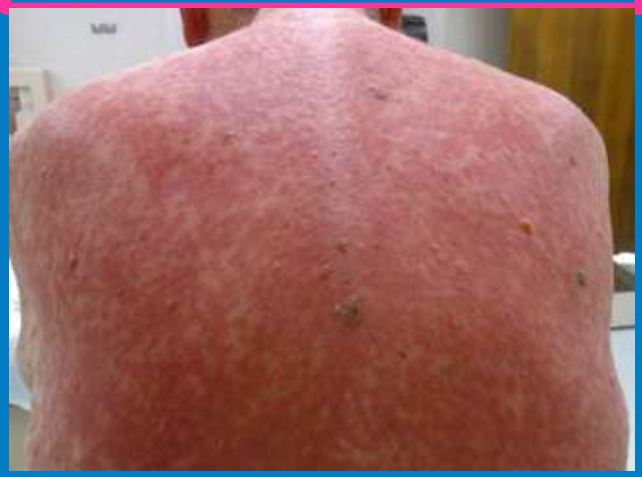
Allopurinol SCARs

SJS



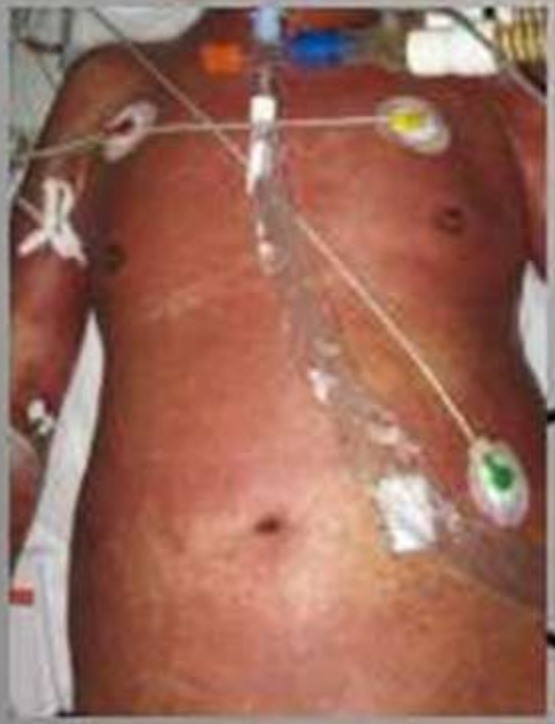
TEN

drug hypersensitivity syndrome



ALLOPURINOL BALANCE

Allopurinol Hypersensitivity Syndrome



Kidney Failure

Allopurinol Hypersensitivity Syndrome

NDT Advance Access published March 10, 2011

Nephrol Dial Transplant (2011) 0: 1–6
doi: 10.1093/ndt/gfr060

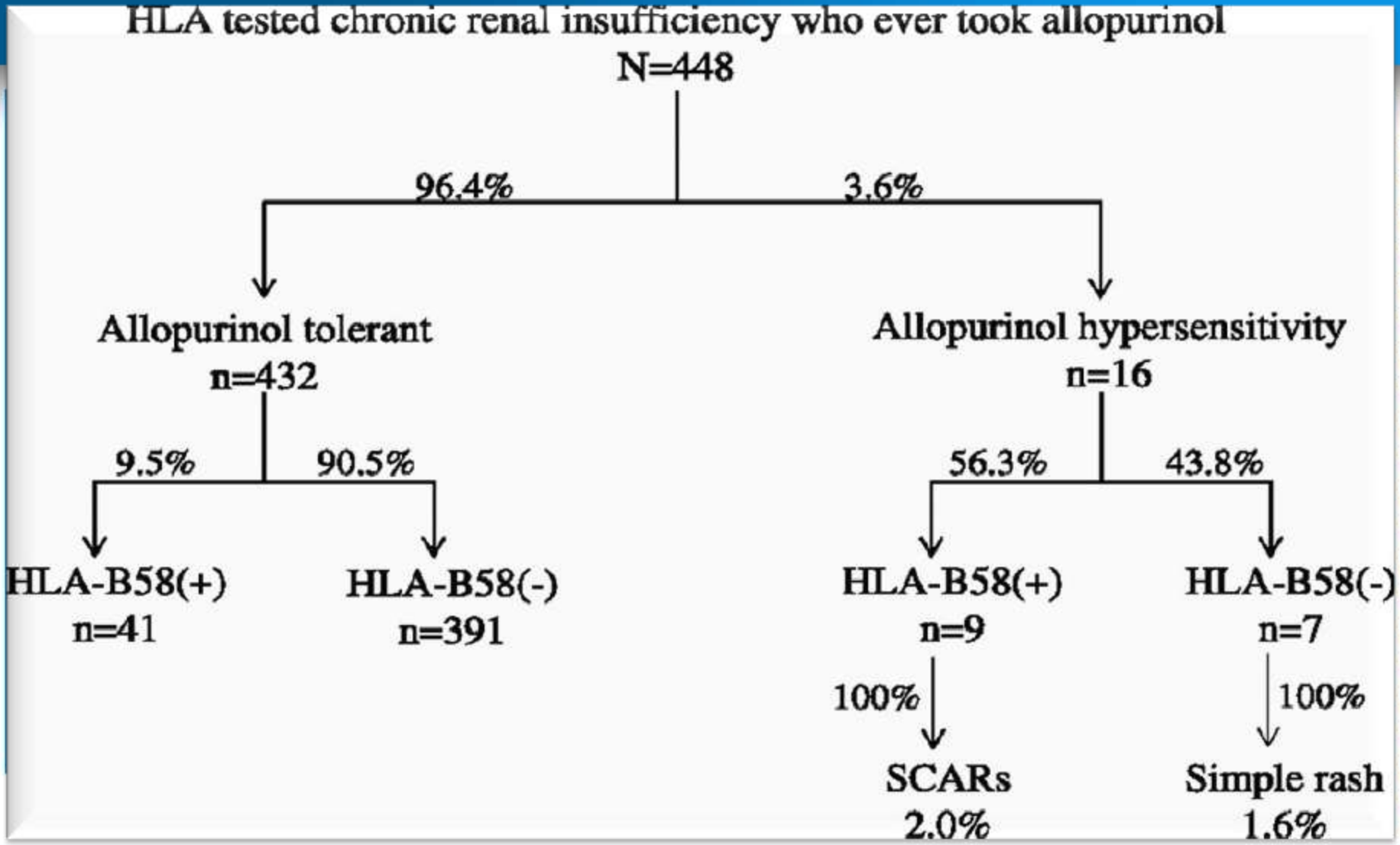
NDT
Nephrology Dialysis Transplantation

Original Article

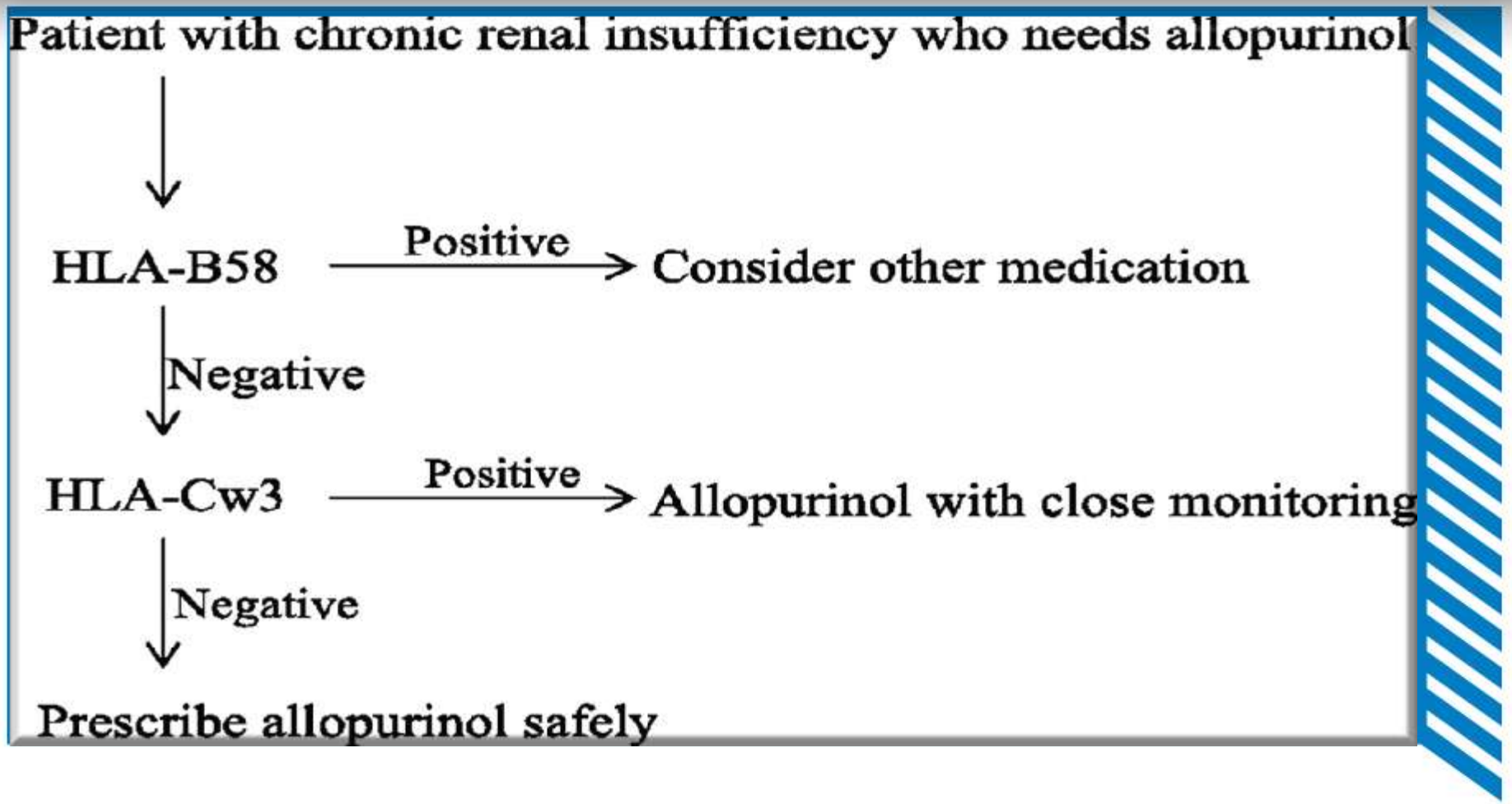
HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency

Jae-Woo Jung[1,2], Woo-Jung Song[1,2], Yon-Su Kim[1], Kwon Wook Joo[1], Kyung Wha Lee[3], Sae-Hoon Kim[2,4], Heung-Woo Park[1,2], Yoon-Seok Chang[2,4], Sang-Heon Cho[1,2], Kyung-Up Min[1,2] and Hye-Ryun Kang[1,2]

Allopurinol Hypersensitivity Syndrome



Allopurinol Hypersensitivity Syndrome



One Approach to Allopurinol Dosing in CKD

Estimated CrCl (ml/min)	Allopurinol Dose
140	400 mg daily
120	350 mg daily
100	300 mg daily
80	250 mg daily
60	200 mg daily
40	150 mg daily
20	100 mg daily
10	100 mg every 2 days
0	100 mg every 3 days

Hande KR 1984 Am J Med 76:47.

Table 3: Comparison of Allopurinol and Rasburicase

Comparator	Allopurinol	Rasburicase
Effect on uric acid	Inhibits uric-acid formation	Decreases uric-acid levels
Onset of action	Days	Hours
Relative efficacy	Weak	Strong
Reported drug interactions	Mercaptopurine, azathioprine (among others)	None identified
Dose adjustments	Necessary in the setting of renal dysfunction	None
Black box warnings	None	Anaphylaxis, hemolysis, methemoglobinemia
Contraindications	None	G6PD deficiency
Available formulations	IV and oral (tablets and extemporaneous suspension)	IV
Relative cost	Inexpensive	Expensive

Table 3. Dosage and Cost of Some Drugs for Chronic Gout

Drug	Dosage	Cost[1]
Allopurinol – generic *Zyloprim* (Prometheus)	100-800 mg/d[2] PO	$15.99 79.99
Febuxostat – *Uloric* (Takeda)	40-80 mg once daily PO	174.55
Pegloticase – *Krystexxa* (Savient)	8 mg IV every 2 weeks	4600.00[3]

1. Cost of 30 days' treatment with 300 mg of allopurinol and 40 mg of febuxostat based on prices at drugstore.com; accessed January 28, 2011. Allopurinol is also available at some discount pharmacies at a cost of $4 for 30 tablets.
2. Doses of 300 mg/day or more should be given in divided doses. Dosage adjustments should be made for those patients with renal impairment.
3. The wholesale acquisition cost (WAC) of a single 8-mg vial is $2300, according to the manufacturer.

Savient (SVNT) Increases Price on KRYSTEXXA to $5,390

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Savient Pharmaceuticals, Inc. (Nasdaq: SVNT) announced today that it increased the price per vial for KRYSTEXXA to $5,390, effective for orders placed after 5:00 p.m. Eastern Standard Time on May 17, 2013. The Company will continue to evaluate the pricing of KRYSTEXXA, as continued substantial price increases will, in light of the current market dynamics for KRYSTEXXA, be necessary in the Company's effort to obtain sufficient revenue from KRYSTEXXA. The Company will have no duty to make public disclosure of price increases.

Hyperuricemia

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (*Not Graded*)